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(54) Title: MODULATORS OF RYANODINE RECEPTORS COMPRISING 2-(ARYL)-4,7-DIOXOBENZOTHIAZOLES AND ANALOGUES THEREOF

(57) Abstract

Compounds, compositions, and methods comprising novel substituted 2-(aryl)-4,7-dioxobenzothiazole derivatives are disclosed.

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MODULATORS OF RYANODINE RECEPTORS COMPRISING 2-(ARYL)-4,7-DIOXOBENZOTHIAZOLES AND ANALOGUES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is based upon, and claims priority to, U.S. Provisional Application Serial No. 60/071,791, filed December 19, 1997, and entitled, "Novel Modulators of Ryanodine Receptors Comprising 2-(Phenyl)-4,7-Dioxobenzothiazoles and Analogues Thereof."

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to novel compounds that modulate ryanodine receptors, as might be particularly useful in pesticides or as a therapeutic agent.

BACKGROUND OF THE INVENTION

For over one-half of a century, the bark from *Ryania speciosa* Vahl, which contains ryanoids, has been used as a component in a natural pesticide known as *Ryania*. During the last three decades, ryanodine, which is the major alkaloid from *Ryania speciosa* Vahl, has aided in the identification, localization, and cloning of three different forms of mammalian ryanodine-sensitive calcium-release channels (ryanodine receptors or CRCs): RyR1, which is predominant in skeletal muscle, RyR2 which is predominant in the heart and the brain, and RyR3 which was first identified in the brain but subsequently found to be ubiquitously distributed, with the highest expression occurring in the diaphragm. Ryanodine was also instrumental in identifying the α and β isoforms of RyR1 in avian and amphibian muscles.

Although ryanodine has been and still continues to be used as a high affinity probe for mammalian and non-mammalian ryanodine receptors, it is well known in the art that this compound is ill-suited for use as a therapeutic agent or as the major component of pesticides for a number of reasons. For example, ryanodine is not only highly toxic to non-vertebrates, as evidenced by the use of *Ryania* as an insecticide, but also to vertebrates. In this respect, studies have shown that 300 nmol/kg i.v. of ryanodine is lethal to rats. To date, the primary target tissue underlying ryanodine's toxic actions is uncertain, but death is due primarily to respiratory muscle paralysis. Also, ryanodine is a complex, hexacyclic, polyhydroxy, diterpene alkaloid (Trinidad and Brazil are the major sources, yields $\leq$ 0.1% w/w of plant tissue).

Most naturally occurring congeners of ryanodine, synthetic precursors of ryanodine, and semi-synthetic ryanoids are undesirable for therapeutic or pesticidal use because they exhibit lower affinities than ryanodine for existing binding sites on the receptors. Also, with the decline in tropical rain forests, the source of this alkaloid is rapidly dwindling and, as a result, the cost of ryanodine has escalated. Finally, ryanodine receptors exhibit an undesirable concentration-dependent biphasic response upon treatment with ryanodine. Because of its extremely slow on and off kinetics from the receptors, many investigators, especially those studying actions at the single channel level, use concentrations of ryanodine significantly higher than its K_d value to study its functional effects. At these high concentrations, ryanodine may open some calcium-release channels but may

undesirably close others, thereby confounding interpretation of the results.

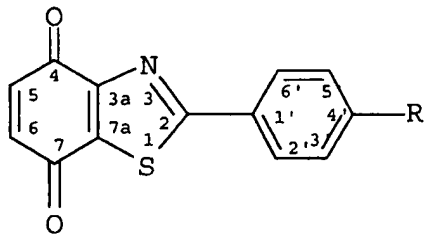
Researchers in the field have long recognized the limitations associated with ryanodine and ryanoids in general. Extensive efforts are ongoing to identify compounds that bind to and selectively activate or deactivate ryanodine receptors.

Although a number of exogenous substances, such as eudostomins, caffeine, dantrolene, halothane and imperatoxins, as well as endogenous ligands, such as calcium and magnesium ions, cyclic adenosine diphosphate-ribose (cADP-ribose), FK binding proteins (FKBP12), and calmodulin, are known to have modulatory effects on ryanodine receptors, their affinities and efficacies vary significantly among the three types of mammalian ryanodine receptors (RyR1, RyR2, and RyR3). In addition, these ligands do not interact at the ryanodine binding site(s) on the receptors. With the exception of eudostomins and imperatoxins, all of these ligands have affinities in the micromolar range.

From the foregoing, it will be appreciated that ryanodine has not been satisfactory for therapeutic uses because of its high mammalian toxicity. Also of disadvantage are the extremely slow association and dissociation kinetics of ryanodine. In addition, it was not possible even to explore the therapeutic potential of selectively activating or deactivating ryanodine receptors because of ryanodine's concentration-dependent biphasic effect on CRCs. It also bears mentioning that total chemical synthesis of ryanodine is beyond the state of the art.

SUMMARY OF THE INVENTION

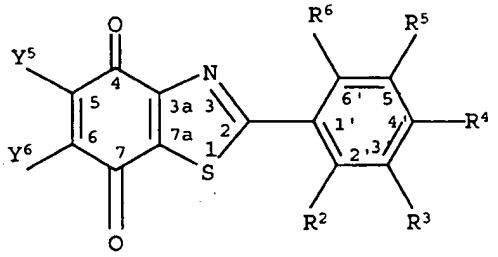
The present invention comprises novel substituted 2-(aryl)-4,7-dioxobenzothiazole derivatives (herein termed "BQTs") given by the formula:



FORMULA I

where R is hydrogen, methyl or a halogen.

In accordance with the present invention, a series of analogues are also provided as characterized by the following formula:



FORMULA II

As seen in Formula II, these analogues can include substitutions on the C_2 phenyl at the 2', 3', 4', 5', and 6' positions denoted as R^2-R^6, as well as substitutions on positions 5 and 6 of the benzoquinone moiety denoted as Y^5 and Y^6.

The substituents on the phenyl moiety will vary from electron donating (for example, alkyl, such as methyl, ethyl, propyl, and butyl) to electron withdrawing functionalities (for example, acyl, cyano, or fluoro), as well as substituents that can modulate the electron density of the phenyl moiety (for example, amino, alkoxy,

such as methoxy and ethoxy, halogen, especially iodo, chloro, and bromo, as well as hydroxy). Functional groups may be inserted into these positions as mono-, di-, tri-, tetra-, or penta- substitutions.

The substituents on the benzoquinone moiety will vary from electron donating (for example, alkyl, such as methyl, ethyl, propyl, and butyl) to electron withdrawing functionalities (for example, acyl, cyano, or fluoro), as well as substituents that can modulate the electron density of the benzoquinone moiety (for example, amino, alkoxy, such as methoxy and ethoxy, cyclic aromatic, halogen, especially iodo, chloro, and bromo, hydroxy, and heterocyclic substituents). Functional groups may be inserted into these positions as mono- or di- substitutions.

Compounds according to the present invention exhibit a very high affinity for binding to ryanodine-sensitive calcium-release channels from muscle (RyRs) and an appreciable ability to alter the patency ("openness") of these channels. Therefore, these compounds (i) are suitable as molecular probes for RyRs, and it is also contemplated that these compounds (ii) have use in beneficially altering the concentrations of intracellular free calcium upon introduction into an organism, thereby ameliorating the underlying etiology for a wide array of cellular pathologies, by a mechanism or mode of action different from those of existing drugs, and (iii) have use as pesticides. Moreover, these compounds are of far simpler structure than ryanodine but carry its pharmacological actions.

In accordance with the present invention, novel ligands with simple chemical structures that bind specifically to and activate endoplasmic/sarcoplasmic

reticulum calcium-release channels (ryanodine receptors) were synthesized. As seen previously, activator-selective ryanoids are less toxic than ryanodine to rats when given intravenously. Since the novel ligands of the present invention preferentially activate ryanodine receptors, it is likely that they are less toxic and can be used to investigate the therapeutic potential of selectively activating or opening ryanodine receptors. In accordance with an aspect of the present invention, it has been also shown that activator-selective ryanoids were more toxic than ryanodine to insects. Taken in concert with data obtained in rats, activating RyRs in accordance with the present invention reduces mammalian toxicity, but increases insect toxicity.

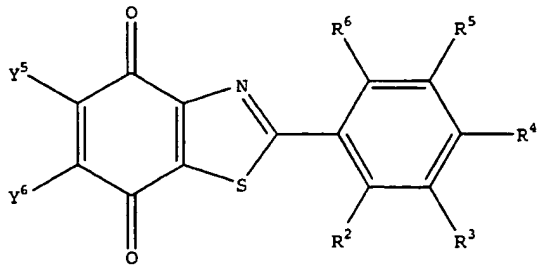
In addition, the compounds of the present invention are molecules of simple chemical structure, and can be easily synthesized from common laboratory reagents, therefore reducing significantly the problem of supply and cost. The simple chemical structures of the compounds of the present invention interact at ryanodine binding sites and activate ryanodine receptors. These compounds have been specifically synthesized to investigate the therapeutic potential of selectively activating ryanodine receptors. In addition, since the compounds of the present invention predominantly activate ryanodine receptors, they are expected to exhibit high insect toxicity, but low mammalian toxicity, thereby making them useful as pesticides.

Brief Description of the Drawing

FIG. 1 illustrates a synthetic scheme for preparing exemplary compounds in accordance with the present invention.

Detailed Description of the Preferred Embodiments

The present invention is drawn to novel 2-(aryl)-4,7-dioxobenzothiazoles (hereinafter "BQT's") of the formula:



wherein R^2-R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents; and Y^5 and Y^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents, or Y^5 and Y^6 together comprise a fused cyclic substituent (fused to the quinone ring at positions 5 and 6) having from 4 to 8 atoms in the ring skeleton (including heteroatoms), defining a carbocyclic or a heterocyclic, aromatic or non-aromatic, ring, optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents; and suitable salts thereof. The compounds of the present invention can be further derivatized with a sugar moiety, for example, but not limited to, a 5 or a 6 membered ring. The sugar is preferably a natural sugar. The derivatization with the sugar could aid the solubilization of the compounds.

Non-aromatic carbocyclic rings include ring systems such as, for example, cyclobutene, cyclobutadiene, cyclopentene, cyclopentadiene, cyclohexene, cycloheptene, cyclooctene, and the like. Aromatic carbocyclic rings include ring systems such as, for example, benzene, naphthalene, and the like. As noted above, the aromatic ring can be optionally substituted, including rings such as, for example, toluene, xylene (ortho, meta, or para), ethylbenzene, isobutylbenzene, n-propylbenzene, and the like. Non-aromatic heterocyclic rings include ring systems such as, for example, piperidine, tetrahydropyridine, pyran, tetrahydrofuran, dihydrofuran, pyrrolidine, and the like. Aromatic heterocyclic rings include ring systems such as, for example, pyridine, pyrimidine, furan, thiophene, oxazole, pyrazole, imidazole, thiazole, and the like.

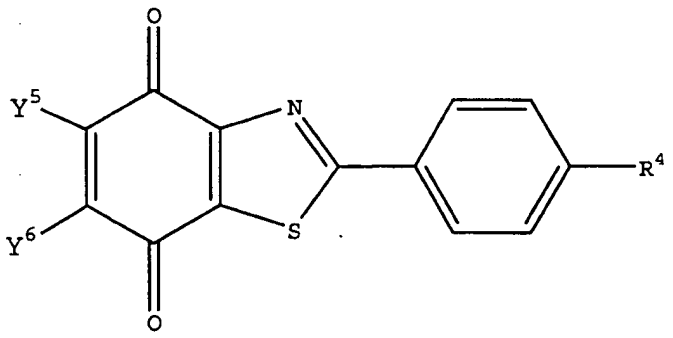
The term "electron donating substituent" as used herein refers to a functional group which has a tendency to donate electron density, including, for example, alkyl substituents (e.g., methyl, propyl, isobutyl), alkenyl substituents (e.g., 2-butenyl), and alkynyl substituents (e.g., propargyl), and the like. As utilized herein, the term "alkyl" means a straight-chain or branched-chain alkyl group which, unless otherwise specified, contains a chain from about 1 to about 20 carbon atoms, preferably from about 1 to about 10 carbon atoms, more preferably from about 1 to about 8 carbon atoms, and even more preferably from about 1 to about 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, octyl, dodecanyl, and the like. Similarly, "alkenyl" and "alkynyl" refer to straight-chain or branched-chain groups which preferably

contain chains from about 1 to about 20 carbon atoms, preferably from about 1 to about 10 carbon atoms, more preferably from about 1 to about 8 carbon atoms, and even more preferably from about 1 to about 6 carbon atoms. The term "electron withdrawing substituent" as used herein refers to a functional group that has a tendency to withdraw electron density, including, for example, cyano, acyl, carbonyl, fluoro, nitro, sulfonyl, trihalomethyl, and the like. The term "electron modulating substituent" as used herein refers to a functional group which has a tendency to modulate electron density, that is, a functional group including, for example, amino, hydroxy, alkoxy, aryl (monocyclic or polycyclic, such as, but not limited to, phenyl and naphthyl) substituents, heterocyclic substituents (including, e.g., examples set forth above for Y^5 and Y^6), halogens, and the like, which has both electron withdrawing and inductive properties, such that the electron modulating substituent can stabilize a cationic (intermediate) in an electrophilic aromatic substitution reaction. Suitable salts include salts derived from acids such as, for example, hydrochloric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, and the like.

The electron donating substituent is preferably an alkyl substituent. The electron withdrawing substituent is preferably a substituent selected from the group consisting of acyl (e.g., acetyl, propionyl, butyryl, isobutyryl, and the like) cyano, nitro, and fluoro, and is more preferably, cyano, nitro, or fluoro. The electron modulating substituent is preferably selected from the group consisting of amino (e.g., NH_2, alkylamino, and dialkylamino, such as, but not limited to,

methylamino, dimethylamino, and the like), alkoxy (preferably C_1-C_{10} alkoxy), halogen, and hydroxy. When Y^5 and Y^6 together comprise a fused cyclic substituent (fused to the quinone ring at positions 5 and 6), there are preferably about 5-7 atoms in the ring skeleton (including heteroatoms), preferably 5 or 6 atoms, and even more preferably 6 atoms. When Y^5 and Y^6 together comprise a fused cyclic substituent, it is preferably a heterocyclic ring, preferably comprising about 5-7 atoms in the ring skeleton (including heteroatoms), more preferably 5 or 6 atoms. When the fused cyclic substituent is a 6 - numbered ring, it is most preferably a pyridine ring.

In a preferred embodiment, the present invention is drawn to a BQT of the formula:



wherein R^4 is selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents; and Y^5 and Y^6 are independently selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents, or Y^5 and Y^6 together comprise a fused cyclic substituent (fused to the quinone ring at positions 5 and 6) having from 4 to 8 atoms in the ring skeleton (including heteroatoms), defining

carbocyclic or heterocyclic, aromatic or non-aromatic, ring, optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents; and salts thereof.

The present invention further provides a pesticidal or therapeutic (pharmaceutical) composition comprising a compound of the present invention and any acceptable carrier therefor. Since the inventive compounds generally do not exhibit high water solubility, carriers such as a form of cyclodextrin and other encapsulating agents, for example, can be used to deliver the inventive compounds and compositions to the desired site(s) of action, as will be apparent to one of ordinary skill in the art.

The compositions of the present invention may be in a pharmaceutical form suitable for oral use such as, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of compositions, and such compositions can contain one or more agents including, for example, sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide a pharmaceutically elegant and/or palatable preparation. Tablets can contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. Such excipients can include, for example, inert diluents such as, for example, calcium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents such as, for

example, maize starch or alginic acid; binding agents such as, for example, starch, gelatine or acacia, and lubricating agents such as, for example, stearic acid or talc. The tablets may be uncoated, or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. A time delay material, for example, glyceryl monostearate or glyceryl distearate, alone or with a wax, may be employed. Formulations for oral use also can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example arachis oil, peanut oil, liquid paraffin or olive oil.

Aqueous suspensions typically contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents, for example, sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia. Dispersing or wetting agents may include natural-occurring phosphatides, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example, polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived

from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate. The aqueous suspensions also can contain one or more preservatives, for example, ethyl or n-propyl p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents such as, for example, sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions can be preserved by the addition of an antioxidant such as, for example, ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, also may be present.

The compositions of the present invention also can be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, for example, olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacantn, naturally-occurring phosphatides, for example

soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters and ethylene oxide, for example polyoxyethylene sorbitan mono-oleate. The emulsions also can contain sweetening and flavoring agents.

The compositions of the present invention can be in the form of syrups and elixirs, which are typically formulated with sweetening agents such as, for example, glycerol, sorbitol or sucrose. Such formulations also can contain a demulcent, a preservative and flavoring and coloring agents.

The compositions can be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleagenous suspension. Suitable suspensions for parenteral administration can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. Formulations suitable for parenteral administration also can include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The sterile injectable preparation can be in the form of a solution or a suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in water or 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed, for example, are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are

conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as, for example, oleic acid find use in the preparation of injectables.

The compounds of the present invention also can be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, for example, cocoa butter and polyethylene glycols. Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, and foams.

Formulations suitable for topical administration may be presented as creams, gels, pastes, or foams, containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

The inventive compounds, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation or as a pesticide. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also can be formulated as pharmaceuticals for non-pressured preparations such as in a nebulizer or an atomizer.

The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile

liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

Any suitable dosage level can be employed in the compositions of the present invention. The dose administered to a pest or animal (in the latter respect, particularly a human), in the context of the present invention should be sufficient to effect a prophylactic, pesticidal, or therapeutic response in the animal over a reasonable time frame. The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. One skilled in the art will recognize that the specific dosage level for any particular patient will depend upon a variety of factors including, for example, the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound. Other factors which effect the specific dosage include, for example, bioavailability, metabolic profile, and the pharmacodynamics associated with the particular compound to be administered in a particular patient. Suitable doses and dosage regimens can be determined by comparisons, for example, with similarly-acting agents or as will be apparent to one of ordinary skill in the art.

The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic response in the animal over a reasonable time frame. The dose will be determined by the strength of the particular composition employed and the condition of the animal, as well as the body weight of the animal to be treated. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound. Other factors which effect the specific dosage include, for example, bioavailability, metabolic profile, and the pharmacodynamics associated with the particular compound to be administered in a particular patient. One skilled in the art will recognize that the specific dosage level for any particular patient will depend upon a variety of factors including, for example, the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, the severity of the symptoms presented prior to or during the course of therapy, and the like.

One skilled in the art will appreciate that suitable methods of administering the compounds and compositions of the present invention to an animal are available, and, although more than one route can be used to administer a particular composition, a particular route can provide a more immediate and more effective reaction than another route.

The present invention further provides a method of altering the concentration of intracellular free calcium in a living organism (e.g., a vertebrate), which method comprises exposing the organism to an intracellular free

calcium concentration altering-effective amount of a compound of the present invention. By way of example, it is contemplated that the inventive compounds and methods will have use in treating diseases (including conditions), such as, but not limited to, congestive heart failure, migraine headaches, hypertension, premature abortions, and Parkinson's and Alzheimer's diseases (particularly at early stages). The compound can be diluted with an acceptable diluent (e.g., a carrier, as described above) for enhancing the uptake of the compound by the organism.

BQTs can also complement ryanodine as *in vitro* probes of ryanodine receptors. Direct comparisons of the effects of BQTs on ryanodine receptors can be made with those of ryanodine.

In order to promote a further understanding and appreciation of the present invention and its attendant advantages, the following specific Examples are provided. It will be understood that these Examples are illustrative and not limiting in nature.

EXAMPLE 1 - CHEMICAL PREPARATION METHODS

BQT #1 (set forth below) was synthesized in four steps, starting with readily available 2,5-dimethoxy aniline using the procedure schematically depicted in Figure 1.

a) Benzoyl amide of 2,5-dimethoxyaniline (2a)

Benzoyl chloride (1.5 mL) was added to a solution of 2,5-dimethoxyaniline (**1a**)(2.0 g, 13.2 mmol) in dry toluene (12 mL) and dry pyridine (10 mL). The solution was heated on a water bath at 60-70 °C for 1 hour. The mixture was cooled to room temperature and poured into 200 mL of water. The two layers were separated and the

aqueous layer was extracted with toluene (3 x 10 mL). The combined toluene layers were dried over $MgSO_4$, filtered, and the toluene removed on a rotary evaporator. Ethyl acetate (40 mL) was then added to the residue and the resultant solution washed with 1M HCl (3 x 10 mL) followed by brine (3 x 10 mL) and then dried over $MgSO_4$. The solution was filtered and the solvent removed by rotary evaporation to yield light brown rock-like crystals (80% yield), m.p. 69° - 71 °C. IR (KBr disc): ν_{max}3336 cm^{-1} and 1656 cm^{-1}.

b) Benzoyl thioamide of 2,5-dimethoxyaniline(3a)

Lawesson's reagent (2.0 g, 4.94 mmol) was stirred in dry toluene (5 mL), to which was added N-2,5-dimethoxyphenylbenzamide (**2a**) (1.0 g, 3.89 mmol) in dry toluene (5 mL). The mixture was heated under an atmosphere of nitrogen at 70-80 °C for 2 hours. The solvent was evaporated and the thioamide was purified by column chromatography [dichloromethane:hexane (3:1)] to yield bright yellow crystals (90% yield), m.p. 58 °C - 61 °C. IR (KBr disc): ν_{max}3385 cm^{-1}, 1597 cm^{-1}, and 1365 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 3.80 (3H,d), 3.85 (3H,d), 6.80 (2H,m), 7.45 (2H,m), 7.85 (2H,m), 9.1 (1H,s), 9.75 (1H,s).

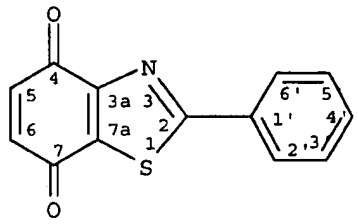
c) 2-Phenyl-4,7-dimethyoxybenzothiazole (4a)

N-2,5-dimethoxyphenylthiobenzamide (**3a**) (3.0 g, 11.25 mmol) was dissolved in freshly prepared 1.5 M aqueous sodium hydroxide (100 mL). Freshly prepared potassium ferricyanide solution (20% aqueous, 30 mL) was added to the cooled solution. The mixture was stirred at room temperature for 24 hours. The precipitate was filtered and then dissolved in concentrated HCl(40 mL). Water (3 x 40 mL) was carefully added. The precipitated thiazole was collected by filtration and purified by column chromatography [dichloromethane:hexane (3:1)] and

then recrystallized from methanol to afford fine needle-like cream-white crystals (80% yield), m.p. 122 °C-124 °C. IR(KBr disc): ν_{max}2988 cm^{-1}, 2939 cm^{-1}, 1560 cm^{-1}, and 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 4.08(3H,s), 3.93(3H,s), 6.80(2H,q), 8.15(2H,m), 7.50(3H,m).

d) 2-Phenyl-4,7-dioxobenzothiazole (BQT#1)

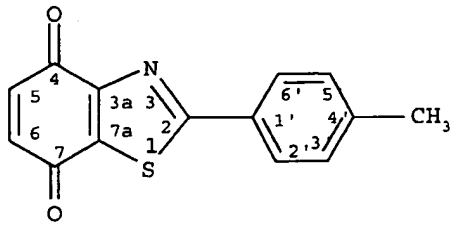
2-Phenyl-4,7-dimethoxybenzothiazole (**4a**)(417 mg, 1.53 mmol) was dissolved in dry acetonitrile (20 mL). To this was added an aqueous solution of ceric ammonium nitrate (3.0 g, 5.47 mmol) in water (15 mL) over 5 minutes. The solution was stirred continuously for 30 minutes at room temperature. The reaction mixture was then extracted with chloroform (3 x 15 mL). The solvent was evaporated to yield an orange-red powder (90% yield), m.p. 198 °C-200 °C. IR(KBr disc): ν_{max}1654 cm^{-1} and 1675 cm^{-1}. ^{1}H-NMR($CDCl_3$): δ 8.09 (2H,d), 7.50 (3H,m), 6.90 (2H,s). IC_{50} value of 400 nM (for RyR1).



(BQT#1)

e) 2-(4-methylphenyl)-4,7-dioxobenzothiazole (BQT#2)

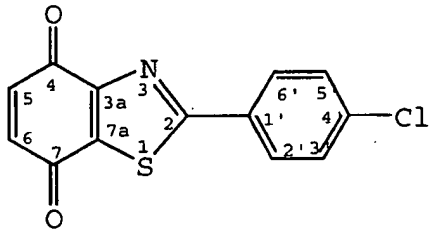
Applying the procedure of Example 1(a)-1(d), except using, as the starting material, 4-methyl benzoyl chloride (p-toluoyl chloride) instead of benzoyl chloride, the BQT #2 compound(set forth below) was prepared. (Yield ~22% from **2b**), m.p. 203 °C-206 °C, IR(KBr disc): ν_{max}1650 cm^{-1}, 1675 cm^{-1}. ^{1}H-NMR($CDCI_3$) δ 2.40 (s,3H); 6.90(s,2H); 7.31 (d,2H); 7.99 (d,2H). IC_{50} value of 275 nM (for RyR1).



(BQT#2)

f) 2-(4-chlorophenyl)-4,7-dioxobenzothiazole(BQT#3)

Applying the procedure of Example 1(a)-1(d), except using, as a starting material, 4-chlorobenzoyl chloride instead of benzoyl chloride, the BQT #3 compound (set forth below) was prepared. (Yield ~40% from **2c**), m.p. 222 °C-224 °C, IR(KBr disc): ν_{max}1650 cm^{-1} and 1675 cm^{-1}. ^{1}HNMR($CDCl_3$): δ 6.98 (s,2H); 7.55 (d,2H), 8.08 (d,2H). IC_{50} value of 210 nM (for RyR1).



(BQT#3)

g) Isomeric [2-phenylthiazolo[4,5-g]quinolinequinones] (BQT#4 and BQT#5)

In this example, the structure-activity relationship studies have been extended to include two isomeric forms of thiazolo[4,5-g]quinolinequinone (BQT#4 and BQT#5, set forth below), i.e., derivatives of BQT#1 which possess a fused para-methyl pyridine ring on the 5 and 6 positions.

In order to prepare isomeric 2-phenylthiazolo[4,5-g]quinolinequinones (BQT #4 and BQT #5), 2 butenal-N,N-dimethylhydrazone (100 mg, 0.89 mmol) was added with stirring to 2-(phenyl)-4,7-dioxobenzothiazole (BQT#1)(200

mg, 0.83 mmol) in dry acetonitrile (10 mL). The mixture was stirred at room temperature for 48 hours. The solvent was removed with a rotary evaporator. The reaction mixture was purified by column chromatography with dichloromethane as the eluent. Two isomeric forms of the Diels-Alder adducts were obtained in total yield of 40%.

BQT#4

m.p. 238 °C-240 °C.

IR(KBr disc): ν_{max}1658 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 2.90 (s,3H), 7.50-7.60 (m,1H), 7.50-7.60 (m,3H), 8.10-8.15 (dd,2H), 8.81 (d,1H).

IC_{50} value of > 10 μM (for RyR1).

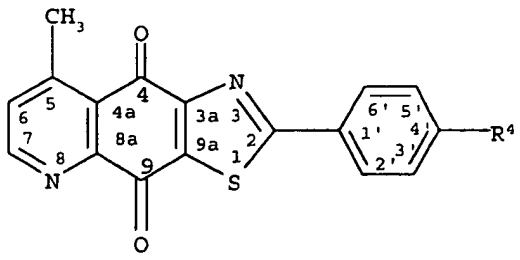
BQT#5

m.p. 255 °C-257 °C.

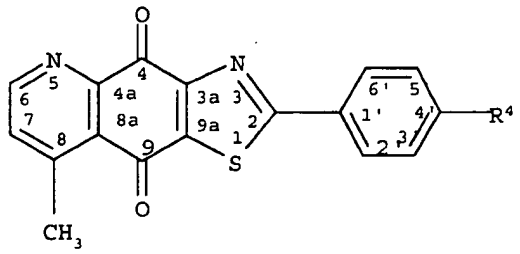
IR (KBr disc): ν_{max} 1658 cm^{-1} and 1678 cm^{-1}.

^{1}H-NMR($CDCl_3$): δ 2.95 (s,3H), 7.40-7.70 (m,4H), 8.20-8.27 (d,2H), 8.95 (d,1H).

IC_{50} value of > 10 μm (for RyR1).



R^4=H (BQT#4)



R^4=H (BQT#5)

EXAMPLE 2 - Pharmacological Findings

a) Binding affinity assays

The binding affinities of BQT#1, BQT#2, BQT#3, BQT#4, BQT#5, and their synthetic precursors were determined in traditional relative binding affinity assays, with results summarized in Table 1. Sarcoplasmic reticulum membrane vesicles (JSRV) from rabbit skeletal muscle (RyR1) (0.1 mg/mL) were incubated in binding buffer (500 mM KCl, 20 mM Tris.HCl, 0.2 mM $CaCl_2$, pH 7.4 at 37 °C) containing 6.7 nM [^{3}H] ryanodine and varying concentrations of BQTs (up to 10,000 nM) for 2 hours at 37°C. At the end of the incubation, the vesicles were filtered through Whatman GF/C filters (0.45 μm) using a cell harvester (Brandel Model M-24R) and the JSRV remaining on the filters were washed with 3 X 3 mL ice-cold binding buffer (pH 7.4 at 0 °C). The filters were

then placed in scintillation cocktail, vortexed, allowed to stand overnight, and the [^{3}H] ryanodine bound to RyRs was quantified by liquid scintillation counting. Non-specific binding was determined simultaneously by incubating JSRV with a concentration of the respective BQT, 10-fold higher than the highest concentration used in the binding assay. Displacement curves, IC_{50} and K_d values were calculated using Microsoft Excel®, CA-Cricket Graph (Version 1.1) and the coupled binding analysis programs EBDA/Ligand and Prism 2.0. The IC_{50} value for each compound was related to that of ryanodine for comparison (Table 1).

b) Functional passive calcium efflux assays

The changes induced by BQT#2 in the ensemble functional patency, i.e., "openness" of RyR1 to calcium flow were assessed by measuring its ability to alter the rates of passive calcium efflux from JSRV previously loaded with $^{45}Ca^{2+}$. In this assay, JSRV (3.5 mg/mL) were incubated in calcium loading buffer (140 mM NaCl, 20 mM HEPES, 1.1 mM Ca^{2+} (spiked with 0.25 μM $^{45}Ca^{2+}$), 0.1 mM EGTA and 1 mM $MgCl_2$, (pH 7.0 at 22 °C)), in the presence of varying concentrations of the BQT #2 (up to 2 mM) for 2 hours at 22 °C. At the end of the incubation time, passive calcium ($^{45}Ca^{2+}$) efflux through RyRs was determined by diluting the vesicles (5 μL) 100-fold into an efflux buffer (140 mM NaCl, 20 mM HEPES, 0.2 mM Ca^{2+} and 1 mM EGTA, pH 7.0 at 22 °C). Efflux was allowed to continue for 3 seconds and then stopped by further diluting the vesicles six-fold into an ice-cold stop solution (140 mM NaCl, 20 mM HEPES, 0.1 mM EGTA, 5 mM $MgCl_2$ and 0.01 mM ruthenium red) and rapidly filtering. The vesicles on the filters were then washed with 3 X 3 mL rinse solution (identical to stop solution except without ruthenium red)

and the $^{45}Ca^{2+}$ remaining inside the vesicles were determined by liquid scintillation counting. In this assay, the ensemble functional patency of RyRs to calcium efflux is inversely related to the amount of calcium ($^{45}Ca^{2+}$) remaining in the vesicles; the lower the amount of $^{45}Ca^{2+}$ remaining in the vesicles the greater the ensemble functional patency of RyRs to calcium efflux and vice versa.

While low μM concentrations of ryanodine open RyRs, permitting increased efflux of $^{45}Ca^{2+}$ from JSRV, and higher concentrations close RyRs, decreasing Ca^{2+} efflux from JSRV, BQT#2 (2-(4-methylphenyl)-4,7-benzoquinonethiazole) did not exhibit a significant ability to close the channels. These data suggest BQT#2 as an activator-selective agonist of ryanodine receptors.

TABLE 1

Name of Compound	IC_{50}(nM) (RyR1)
Ryanodine (reference compound)	6.2 ± 0.1
2-(phenyl)-4,7-dimethoxybenzothiazole	>10000
2-(phenyl)-4,7-dioxobenzothiazole (BQT#1)	400.0 ± 10.5
2-(4-methylphenyl)-4,7-dimethoxybenzothiazole	>10000
2-(4-methylphenyl)-4,7-dioxobenzothiazole (BQT#2)	275.0 ± 13.2
2-(4-chlorophenyl)-4,7-dimethoxybenzothiazole	>10000
2-(4-chlorophenyl)-4,7-dioxobenzothiazole (BQT#3)	210.0 ± 10.8
4-methyl-2-phenylthiazolo[4,5-g]quinoline-5,8-dione(BQT#4)	>10,000
4-methyl-2-(phenyl)thiazolo[5,4-g]quinoline-5,8-dione(BQT#5)	>10,000

Electron withdrawing groups, electron donating groups, and electron modulating groups can be substituted for Y^5 and Y^6 by using synthetic methods that are available to those of ordinary skill in the art. Strictly by way of example, desired substituents can be introduced at Y^5 and/or Y^6 by way of the synthesis

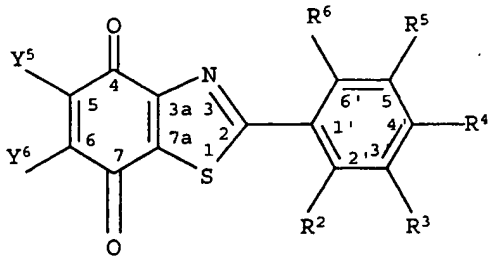
illustrated in FIG. 1, for example, by replacing 2,5-dimethoxy aniline with a suitably substituted 2,5-dimethoxy aniline. Similarly, electron donating groups, electron withdrawing groups, and electron modulating groups can be substituted for R^2-R^6 by using synthetic methods that are available to those of ordinary skill in the art. For example, desired substituents can be introduced at R^2-R^6 by way of the synthesis depicted in FIG. 1, for example, by substituting reactants (e.g., benzoyl chloride, p-toluoyl chloride, or p-methyl benzoyl chloride) with suitably substituted analogues of such reactants.

It is to be noted that alternative methods for making the compounds of the present invention may be employed. For example, as will be appreciated by one of ordinary skill in the art, depending on the desired substitution, 2-(substituted phenyl)-4,7-dimethoxybenzothiazole, a key intermediate in the synthesis of 2-(substituted)-4,7,-dioxobenzothiazoles, can also be synthesized starting from substituted 2-aminothiophenol hydrochlorides instead of substituted anilines depending upon the availability of reagents. This procedure eliminates two steps in the synthetic scheme mentioned above. As one of ordinary skill in the art will appreciate, the fewer the synthetic steps, the greater the yield of product of interest.

While the preferred embodiments of the invention have been disclosed, it should be appreciated that the invention is susceptible to modification without departing from the spirit of the invention or the scope of the following claims.

What Is Claimed Is:

1. A compound characterized by the formula:



wherein R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents; and wherein Y^5 or Y^6 are selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents, or Y^5 and Y^6 together comprise a fused cyclic substituent, fused at positions 5 and 6 of the quinone ring, said cyclic substituent having from 4 to 8 atoms in the ring skeleton thereof, wherein said fused cyclic substituent defines a carbocyclic or a heterocyclic aromatic or non-aromatic ring optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents; a sugar derivative thereof; or any suitable salt thereof.

2. A compound as defined in claim 1, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is an electron donating substituent selected from the group consisting of alkyl, alkenyl and alkynyl.

3. A compound as defined in claim 1, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is an electron donating substituent selected from an alkyl.

4. A compound as defined in claim 1, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is an electron withdrawing substituent selected from the group consisting of acyl, carbonyl, nitro, sulfonyl, trihalomethyl, cyano, and fluoro.

5. A compound as defined in claim 1, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is an electron withdrawing substituent selected from the group consisting of acyl, cyano, and fluoro.

6. A compound as defined in claim 1, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is a substituent that can modulate the electron density of the phenyl moiety and is selected from the group consisting of amino, alkoxy, halogen, aryl, heterocyclic, and hydroxy.

7. A compound as defined in claim 1, wherein at least one of R^2, R^3, R^4, R^5, R^6 is a substituent that can modulate the electron density of the phenyl moiety and is selected from the group consisting of amino, alkoxy, halogen, and hydroxy.

8. A compound as defined in claim 1, wherein at least one of Y^5 and Y^6 is an electron donating substituent selected from the group consisting of alkyl, alkenyl, and alkynyl.

9. A compound as defined in claim 1, wherein at least one of Y^5 and Y^6 is an electron donating substituent selected from an alkyl.

10. A compound as defined in claim 1, wherein at least one of Y^5 and Y^6 is an electron withdrawing substituent selected from the group consisting of acyl,

carbonyl, nitro, sulfonyl, trihalomethyl, cyano, and fluoro.

11. A compound as defined in claim 1, wherein at least one of Y^5 and Y^6 is an electron withdrawing substituent selected from the group consisting of acyl, cyano, and fluoro.

12. A compound as defined in claim 1, wherein at least one of Y^5 and Y^6 is a substituent that can modulate the electron density of the benzoquinone moiety and is selected from the group consisting of amino, alkoxy, halogen, hydroxy, cyclic aromatic, and heterocyclic substituents.

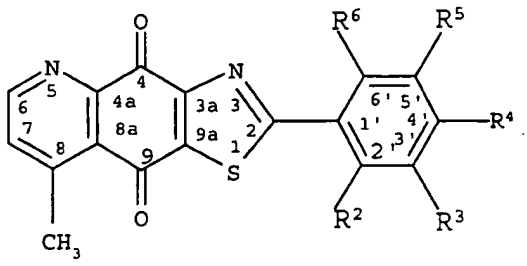
13. A compound as defined in claim 1, wherein Y^5 and Y^6 together comprise a fused cyclic substituent selected from the group consisting of cyclobutene, cyclobutadiene, cyclopentene, cyclopentadiene, cyclohexene, cycloheptene, cyclooctene, benzene, naphthalene, piperidine, pyridine, tetrahydrofuran, pyrrolidine, tetrahydropyridine, pyran, dihydrofuran, furan, thiophene, oxazole, pyrazole, pyrimidine, imidazole, and thiazole.

14. A compound as defined in claim 1, wherein R^2-R^6 and Y^5-Y^6 are hydrogen.

15. A compound as defined in claim 1, wherein Y^5, Y^6, R^2, R^3, R^5, and R^6 are hydrogen, and R^4 is methyl.

16. A compound as defined in claim 1, wherein Y^5, Y^6, R^2, R^3, R^5, and R^6 are hydrogen, and R^4 is chloride.

17. A compound as defined in claim 1 characterized by the formula

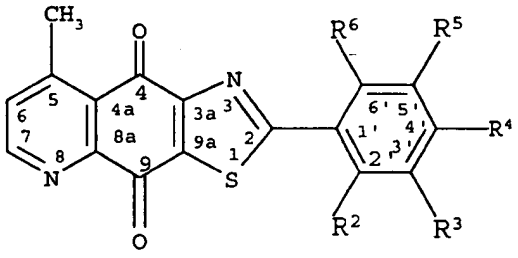


wherein R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents, and wherein the pyridine ring fused to the quinone ring is optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents.

18. A compound as defined in claim 17, wherein R^2, R^3, R^5, and R^6 are hydrogen, and wherein R^4 is selected from the group consisting of hydrogen, methyl, and halogens.

19. A compound as defined in claim 18, wherein R^4 is hydrogen.

20. A compound as defined in claim 1 characterized by the formula



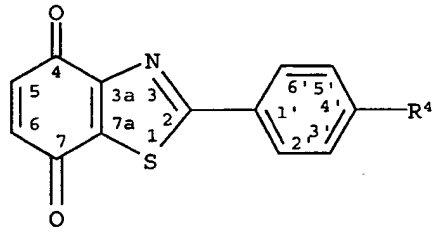
wherein R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents, and wherein the pyridine ring fused to the quinone ring is optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron

withdrawing substituents, and electron modulating substituents.

21. A compound as defined in claim 20, wherein R^2, R^3, R^5, and R^6 are hydrogen, and wherein R^4 is selected from the group consisting of hydrogen, methyl, and halogens.

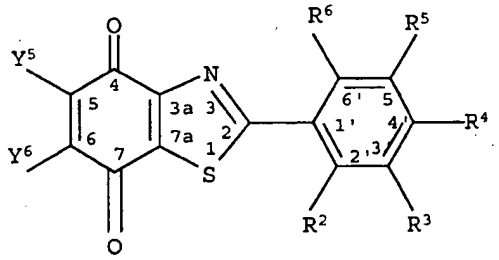
22. A compound as defined in claim 21, wherein R^4 is hydrogen.

23. A compound characterized by the formula



wherein R^4 is selected from the group consisting of hydrogen, methyl, and halogens.

24. A pesticidal composition comprising a compound characterized by the formula



wherein R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents; and wherein Y^5 or Y^6 are selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents,

and electron modulating substituents, or Y^5 and Y^6 together comprise a fused cyclic substituent, fused at positions 5 and 6 of the quinone ring, said cyclic substituent having from 4 to 8 atoms in the ring skeleton thereof, wherein said fused cyclic substituent defines a carbocyclic or a heterocyclic aromatic or non-aromatic ring optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents and electron modulating substituents, or a sugar derivative thereof, or a suitable salt thereof; and an acceptable carrier therefor.

25. A composition as defined in claim 24, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is an electron donating substituent selected from the group consisting of alkyl, alkenyl, and alkynyl.

26. A composition as defined in claim 24, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is an electron withdrawing substituent selected from the group consisting of acyl, carbonyl, nitro, sulfonyl, trihalomethyl, cyano, and fluoro.

27. A composition as defined in claim 24, wherein at least one of R^2, R^3, R^4, R^5, and R^6 is a substituent that can modulate the electron density of the phenyl moiety and is selected from the group consisting of amino, alkoxy, halogen, and hydroxy.

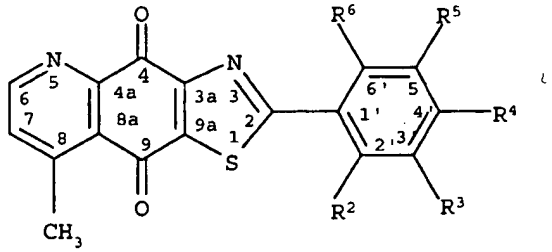
28. A composition as defined in claim 24, wherein at least one of Y^5 and Y^6 is an electron donating substituent selected from the group consisting of alkyl.

29. A composition as defined in claim 24, wherein at least one of Y^5 and Y^6 is an electron withdrawing substituent selected from the group consisting of acyl,

cyano, carbonyl, nitro, sulfonyl, trihalomethyl, and fluoro.

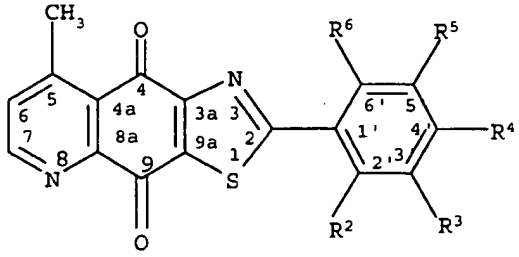
30. A composition as defined in claim 24, wherein at least one of Y^5 and Y^6 is a substituent that can modulate the electron density of the benzoquinone moiety and is selected from the group consisting of amino, alkoxy, halogen, hydroxy, cyclic aromatic, and heterocyclic substituents.

31. A composition as defined in claim 24, wherein the compound is characterized by the formula:



wherein R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents, and wherein the pyridine ring fused to the quinone ring is optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents.

32. A composition as defined in claim 24, wherein the compound is characterized by the formula



wherein R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, electron donating substituents, electron withdrawing substituents, and electron modulating substituents, and wherein the pyridine ring fused to the quinone ring is optionally substituted with a substituent selected from the group consisting of electron donating substituents, electron withdrawing substituents, and electron modulating substituents.

33. A method for altering the concentration of intracellular free calcium in a living organism in order to treat a disease comprising the step of:

exposing the organism to an intracellular free calcium concentration altering-effective amount of a compound of any one of claims 1 to 23.

34. A method as defined in claim 33, wherein said disease is selected from the group consisting of congestive heart failure, migraine headache, hypertension, premature abortion, Parkinson's disease, and Alzheimer's disease.

35. A method as defined in claim 33 further comprising the step of diluting the compound with an acceptable diluent that enhances the uptake of the compound by the organism.

36. A method as defined in claim 35, wherein said diluent comprises an encapsulating agent.

37. A method as defined in claim 36, wherein said encapsulating agent comprises cyclodextrin.

38. A pharmaceutical composition comprising a compound of any one of claims 1-23 and an acceptable carrier therefor.

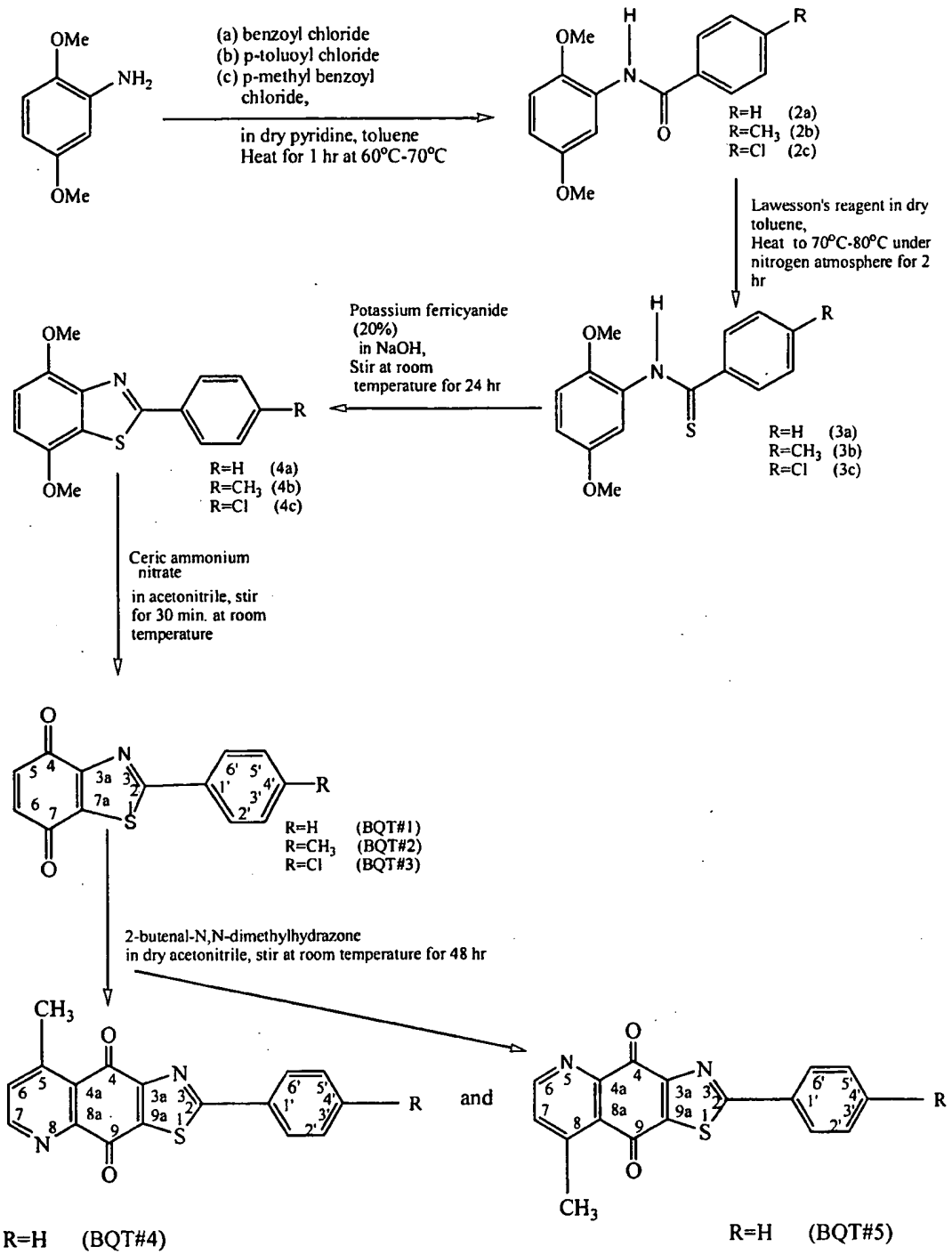

(a) benzoyl chloride
(b) p-toluoyl chloride
(c) p-methyl benzoyl chloride,
in dry pyridine, toluene
Heat for 1 hr at 60°C-70°C
R=H (2a)
R=CH3 (2b)
R=Cl (2c)
Lawesson's reagent in dry toluene,
Heat to 70°C-80°C under nitrogen atmosphere for 2 hr
Potassium ferricyanide (20%) in NaOH,
Stir at room temperature for 24 hr
R=H (3a)
R=CH3 (3b)
R=Cl (3c)
R=H (4a)
R=CH3 (4b)
R=Cl (4c)
Ceric ammonium nitrate
in acetonitrile, stir for 30 min. at room temperature
R=H (BQT#1)
R=CH3 (BQT#2)
R=Cl (BQT#3)
2-butenal-N,N-dimethylhydrazone
in dry acetonitrile, stir at room temperature for 48 hr
and
R=H (BQT#4)
R=H (BQT#5)

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27002

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44, 31/47, 31/425; C07D 277/66, 513/04
US CL :514/293, 367; 546/83; 548/178
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/293, 367; 546/83; 548/178

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/21710 A1 (LABORATOIRE INNOTHERA) 19 June 1997, pages 2-5; pages 42-44, claims 1-7, 10-16, 24.	1-32, 38
X	WO 97/21684 A1 (LABORATOIRE INNOTHERA, SOCIETE ANONYME) 19 June 1997, page 1-8; pages 114-120, claims 1, 13-16, 23-28, 49-52, 65, 70.	1-14, 24-30, 38
X	KATRITZKY et al. Some novel quinone-type dyes containing naphthoquinone and related fused ring systems. J. Heterocyclic Chem. May-June 1988, Vol. 25, pages 901-906, especiallly page 902, compound 14.	1, 6, 13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 FEBRUARY 1999	Date of mailing of the international search report 25 MAR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN HUANG Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/27002

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 106, No. 26, 29 June 1987 (Columbus. OH, USA), page 82, column 2, the abstract No. 215502h, SUGANUMA, H. 'Naphtho[2,3-d]thiozole-4, 9-diones.' Jpn. Kokai Tokkyo Koho JP 61,251, 675, 08 November 1986, abstract.	1, 4, 5, 13
X	Chem. abstr., Vol. 78, No. 1, 08 January 1973 (Columbus. OH, USA), page 350, column 2, the abstract No. 4178x, LUK'YANOV, A.V. et al. 'Heterocyclic quinones. VII. 2-phenylbenzothiazole quinones.' Khim. Geterotsikl. Soedin. 1971, No. 3, 190-193 (Russ), abstract.	1, 12
X	Chem. abstr., Vol. 67, No. 3, 17, July 1967 (Columbus. OH, USA), page 1088, column 2, the abstract No. 11230f, BABU, B.H. et al. 'Synthesis of some substituted naphtho[2,3-d]thiazole-4,9-diones as potential fungicides.' Curr. Sci. 1967, 36(7), 176 (Eng.), abstract	1, 6, 7, 13, 24, 27, 28, 38